REMARKS

Following entry of this amendment, claims 1-11, 21-40, and 55-73 will be pending in this application. Claim 1 is currently amended, and new claims 66-73 are added. Support for the amendments and new claims can be found throughout the specification as filed, e.g., at paragraph [0040]. No new matter has been added.

35 USC § 112, first paragraph

Claims 1-3, 10, 11, and 57-65 were rejected as allegedly not enabled for the full scope of the claims. The Office action states (at page 3) that "the specification, while being enabling for certain specific concentration of CO effective to treat hemorrhagic shock, does not reasonably provide enablement for all concentration CO effective to treat hemorrhagic shock." Applicants respectfully traverse the rejection.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731,8 USPQ2d 1400 (Fed. Cir. 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" *Wands*, 8 USPQ2d 1404. Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Wands*, 8 USPQ2d 1404. The factors to be considered in determining whether undue experimentation is required include: the quantity of experimentation necessary, the amount or direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

The Nature of the Invention and the Scope of the Claims

The claims are directed to methods of treating hemorrhagic shock using a pharmaceutical composition comprising carbon monoxide. Applicants have amended claim 1 to recite that the pharmaceutical composition comprises carbon monoxide at a concentration of about 10 ppm to about 3,000 ppm. Dependent claims recite additional concentrations and ranges.

The State of the Art and Predictability of the Art

The Office action relies on Omaye (Toxicol., 180:139-150, 200) as evidence that CO is allegedly "toxic" at 70 ppm. The Office contends that undue experimentation would be required to practice the claimed invention because:

> One of ordinary skill in the art would first need to determine what concentration of CO to use that would not provide toxicity since applicants envision concentrations of 10-3000 ppm and Omaye discloses that CO levels of 70 ppm is toxic ands the claims is open ended to any amount of CO.

Office action at page 5. The Office appears to rely on Table 2 (page 156) of Omaye to support its assertion that "70 ppm is toxic." However, Table 2 does not teach that 70 ppm of CO causes physiological effects under all conditions. Omaye states that "Table 2 lists examples of ambient CO concentrations, estimated carboxyhemoglobin levels that might result as steady-state exposure, and related human health effects" (p. 144, col. 1). That is, the effects listed in Table 2 are the result of long-term exposure to the indicated concentrations of CO, whereas the specification also contemplates more limited CO exposure. Omaye further teaches that "[e]ffects of CO exposure vary with the concentration and duration" (p. 144, col. 1), and total CO exposure is reflected by carboxyhemoglobin levels (the percentage of hemoglobin in a subject's blood bound by CO rather than oxygen). According to Omaye, most subjects are "asymptomatic" below carboxyhemoglobin (COHb) levels of 10%" (p. 144, col. 1). Because Omaye teaches that the CO dosage received depends on both the concentration of CO inhaled and the duration of exposure, the art clearly understood that concentrations of 70 ppm or higher could be administered to individuals for limited periods of time without significant ill effects.

Further, applicants deny that even the steady-state effects of 70 ppm CO as disclosed by Omaye would deter one skilled in the art from administering CO because it would be too "toxic." Omaye states that the effects of chronic exposure to 70 ppm CO (corresponding to a COHb level of 10%) are "exhaustion in healthy people, more angina in patients, [and] headaches" (Table 2). Doctors administering CO to patients experiencing hemorrhagic shock would clearly be able to weigh any effects such as "exhaustion" or "headaches" (or potentially greater adverse effects) against the therapeutic value of CO in treating hemorrhagic shock, which can lead to multiple organ failure and death.

The prior art also demonstrates that CO exposure (measured as COHb level) of an individual administered a specified amount of CO for a period of time (and any related physiological effect) is highly predictable. Because CO is often viewed as a potential environmental toxin, CO exposure has been extensively studied for decades. As one example, Stewart, 1974, Scand. J. Respir. Dis. Suppl. 91:56-62 (previously submitted), states that "the amount of carbon monoxide absorbed during exposure is highly predictable," and provides a chart showing predicted and experimental values of COHb accumulation over time for various CO concentrations (see Figure 1). At an ambient concentration of 100 ppm CO (higher than the 70 ppm level the Office contends is "toxic"), individuals do not reach a 10% COHb level (below which Omaye indicates that subjects are "asymptomatic") until after more than five hours of continuous exposure. One could administer a large concentration of CO for a short period of time or a small concentration of CO for a long period of time and achieve the same level of CO exposure, as measured by COHb levels. For example, referring to Fig. 1 of Stewart, a patient exposed to 50 ppm CO for 3 hours would have a COHb level of 5%. At a concentration of 1000 ppm, about 10 minutes would be required to achieve an equivalent 5% COHb level. One of skill in the art would appreciate that the "amount" of a pharmaceutical composition comprising CO that is administered by inhalation will depend not only on the concentration of CO inhaled but also the duration of inhalation, and that both variables (concentration and duration) can be adjusted to provide a proper dosage.

Working Examples and Guidance Presented

At page 5, the Office action states: "The working examples fail to provide any amount of CO useable in the invention, and by implication then refers back to the amounts disclosed in paragraph [0040]." On the contrary, the specification provides working examples of CO's protective effect against hemorrhagic shock (see Example 1). Applicants exposed mice to 250 ppm CO for either 6.5 hours during hemorrhagic shock and resuscitation or for 4 hours during only the resuscitation period. This treatment prevented multiple organ injury in the rodent model of HS/R. Even though the concentration of CO used was higher than 70 ppm, the exposure was for a specified period time (as opposed to Omaye's Table 2, which lists effects of ambient, steady-state exposure to 70 ppm CO). One skilled in the art would be able to extrapolate from this example, using the additional guidance in the specification and knowledge in the art, to determine safe and effective dosages of CO to treat hemorrhagic shock.

Furthermore, the specification provides ample guidance that affirms the general knowledge in the art concerning the administration of CO. The specification teaches that CO can be administered at various concentrations "intermittently or continuously" (paragraph [0040]). The specification also contemplates that higher concentrations of CO can be administered for shorter periods of time to achieve a therapeutic effect:

> In a given day, CO can be administered continuously for the entire day, or intermittently, e.g., a single whiff of CO per day (where a high concentration is used), or for up to 23 hours per day, e.g., up to 20, 15, 12, 10, 6, 3, or 2 hours per day, or up to 1 hour per day.

Specification, paragraph [0040]. Further, the specification teaches methods of monitoring a patient's CO level by observing "(1) carboxyhemoglobin (COHb), which can be measured in venous blood, and (2) exhaled CO collected from a side port of the ventilator" (paragraph [0058]). The specification also teaches that "CO exposure can be adjusted based upon the patient's health status and on the basis of the markers" (paragraph [0058]).

The Relative Skill of Those in the Art and the Quantity of Experimentation Necessary

The relative skill of those in the art at the time of filing would have been high. The relevant individual would have been a health care practitioner, e.g., a physician. Applicants submit that health care practitioners at the priority date had a high level of skill in administering drugs (even potentially toxic ones) to patients. To illustrate, one could point to any number of highly toxic compounds, such as cancer chemotherapeutics, inhaled oxygen (which can cause oxidative stress and lung damage), inhaled anesthetic gases, and inhaled nitric oxide, all of which can be dangerous in overly high doses. These substances are routinely successfully administered by physicians of ordinary skill.

The Office action states (at page 5) that "[t]he quantity of experimentation needed is undue experimentation." Applicants submit that this summary conclusion is inappropriate to begin discussion of an individual *Wands* factor. See MPEP § 2164.06 ("The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether 'undue experimentation' is required to make and use the invention."). The Office action goes on to state that:

> One of ordinary skill in the art would first need to determine what concentration of CO to use that would not provide toxicity since applicants envision concentrations of 10-3000 ppm and Omaye discloses that CO levels of 70 ppm is toxic ands the claims is open ended to any amount of CO.

Office action at page 5. As demonstrated above, those skilled in the art at the time of filing appreciated that CO dosage depends not only on the concentration of CO, but also on the timing of the exposure. Those skilled in the art were also well aware of any physiological effects stemming from different levels of CO exposure. Therefore, very little experimentation would be required to determine safe amounts and timing of CO administration. Some experimentation may have been required to determine optimal effective dosages, but this determination is merely routine in the context of pharmaceutical testing.

Applicants submit that any experimentation required to perform the claimed methods would be merely routine, and not undue. The art at the time of filing clearly acknowledged that CO exposure depends not only on the concentration of CO, but also on the length of time

exposed. Such factors predictably determine COHb levels in an exposed subject, and such COHb levels correlate to known and predictable physiological effects. One skilled in the art could predictably administer a high concentration of CO for a short period of time or a lower concentration of CO for a longer period of time to achieve the same effect. No undue experimentation would have been required to determine "safe" amounts of CO to administer, because the art clearly understood the physiological effects of various levels of CO exposure. Adverse effects could be acceptable relative to the beneficial effect of CO to alleviate systemic organ and tissue damage due to hemorrhagic shock. Additionally, the specification provides working examples of CO's effect in a rodent model, and also provides significant guidance in the form of suggested concentration and timing of CO administration. Based on the advanced state of the art regarding knowledge of CO effects, the known predictability of CO administration, the high level of skill of those in the art in administration of potentially toxic drugs (including inhaled gases), the minimal experimentation necessary to determine "safe" dosages, the working examples, and the significant guidance in the specification, applicants submit that the claims are enabled for their full breadth. Applicants therefore request reconsideration and withdrawal of the rejection for alleged lack of enablement.

35 USC § 103

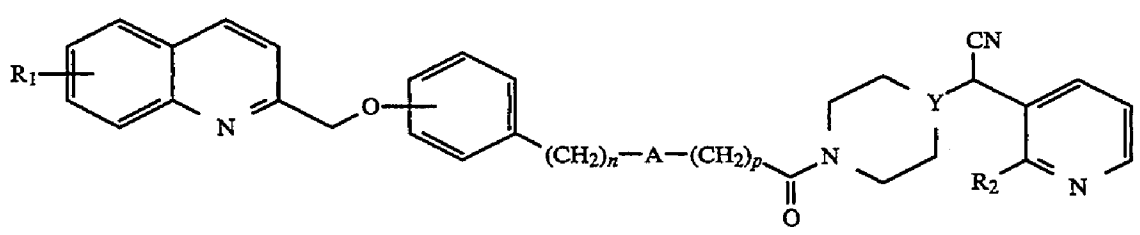
Claims 1 and 3 were rejected as allegedly unpatentable over Fujita et al., Nature Med., 7:598-604, 2001 ("Fujita") or Pinsky et al., US 2005/0048133 ("Pinsky") in view of Carceller et al., US 5,420,131 ("Carceller") or Neely, US 5,504,090 ("Neely"). The Office action alleges that Fujita and Pinsky each teach "treating ischemic injury" and acknowledges that neither publication teaches "treating hemorrhagic shock" (pages 7 and 8). The Office action states (at pages 7 and 8) that:

> [I]schemia and hemorrhagic shock have been known to be treated by the same compositions. For example, Neely teaches method of treating ischemia and reperfusion, sepsis, anaphylaxis, hemorrhagic shock and trauma in patients in need thereof with the inventive composition of Neely (see column 6, lines 24-29). Also, Carceller treats septic shock, anaphylactic shock, hemorrhagic shock

> and myocardial ischemia in a mammal in need thereof by administering an effective amount of the compound of Carceller (see claim 13).
>
> Therefore, taking the teaching of Fujita [or Pinsky] and Carceller or Neely, one having ordinary skill in the art at the time the invention was made would have reasonable expectation of success that administration of the composition comprising CO to a mammal/subject in need thereof would effectively treat ischemic injuries or hemorrhagic shock since these conditions have been known to be treatable by the same compositions or compounds.

Applicants disagree that one of ordinary skill would have been motivated, in view of any combination of Fujita, Pinsky, Carceller, and Neely, to use carbon monoxide to treat hemorrhagic shock with any reasonable expectation of success. As the Office action admits, neither Fujita nor Pinsky teaches treatment of hemorrhagic shock. Neither Carceller nor Neely, alone or in combination, remedy the deficiencies of Fujita and Pinsky. Carceller and Neely provide no disclosure related to carbon monoxide, and the active agents disclosed in Carceller and Neely share no chemical similarity with carbon monoxide. Therefore, one of ordinary skill would not have been motivated to use carbon monoxide in the methods of treating hemorrhagic shock disclosed in Carceller and Neely.

Carceller and Neely disclose the use of molecules that are chemically distinct from carbon monoxide. Carbon monoxide is a diatomic molecule consisting of one atom of carbon bound to one atom of oxygen. The molecules disclosed by Carceller are cyanomethylpyridine derivatives of the general formula:



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Neely discloses the use of selective A_1 adenosine receptor agonists and provides as examples xanthine derivatives and 7-deaza-2-phenyladenine compounds (see col. 6, l. 63, to col. 7, l. 10). The compounds disclosed in Carceller and Neely are small molecules comprising one or more ring structures, and they share no obvious chemical similarity with carbon monoxide.

Because there is no disclosed chemical similarity between carbon monoxide and the compounds disclosed in Carceller and Neely, one of ordinary skill would not have been motivated to use carbon monoxide to treat hemorrhagic shock based on the disclosures of Fujita, Pinsky, Carceller, and Neely, alone or in any combination. The simple fact that molecules that are chemically unrelated to carbon monoxide may have been disclosed as useful for treating both ischemia-reperfusion organ injury and hemorrhagic shock does not indicate that carbon monoxide would also have been expected to treat hemorrhagic shock with any reasonable expectation of success. Applicants therefore request reconsideration and withdrawal of the rejection for alleged obviousness.

Claims 1, 2, 10, 11, and 57-65 were rejected as being allegedly unpatentable over Fujita or Pinsky in view of Carceller or Neely, as applied to claims 1 and 3 above, and further in view of Peitzman et al., Curr. Probl. Surg., 1995, 32: 925-1002, abstract ("Peitzman"). The rejection over Fujita or Pinsky in view of Carceller or Neely is discussed above. Peitzman is provided by the Office apparently for the limitation of blood transfusion. The Office has not alleged that Peitzman provides and Peitzman in fact provides no teaching or suggestion of the use of CO for treatment of hemorrhagic shock. Therefore, Peitzman fails to remedy the deficiencies of Fujita, Pinsky, Carceller, and Neely. Therefore, none of Fujita, Pinsky, Carceller, Neely, or Peitzman, alone or in combination, would render the claims obvious. Therefore, the claims are patentable over either Fujita or Pinsky in combination with any of Carceller, Neely, and Peitzman, and applicants request reconsideration and withdrawal of the rejection.

Claims 1, 55, and 56 were rejected as allegedly being unpatentable over Fujita or Pinsky in view of Carceller or Neely, as applied to claims 1 and 3 above, and further in view of Bach et al., US 2003/0039638 ("Bach"). The rejection over Fujita or Pinsky in view of Carceller or Neely is discussed above. Bach is apparently provided by the Office for the limitation of carbon monoxide at a concentration of 250 ppm. However, Bach does not remedy the deficiencies of Fujita, Pinsky, Carceller, and Neely. Therefore, none of Fujita, Pinsky, Carceller, Neely, or

Bach, alone or in combination, would render the claims obvious. Therefore, the claims are patentable over either Fujita or Pinsky in combination with any of Carceller, Neely, and Bach, and applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants submit that the pending claims are allowable and request early and favorable action thereon. Applicants do not concede any positions of the Office that are not expressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

This response is being submitted along with a Petition for Extension of Time and the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14022-0011001.

Respectfully submitted,

Date: June 4, 2010

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